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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/242,657	02/19/1999	PETER RUHDAL JENSEN	55411.000002	1335

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/242,657	JENSEN ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-11,13-18,21-23,25 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *22* is/are allowed.

6)☒ Claim(s) *1-4,6-11,13-18,21,23,25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/23/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application on 5/28/2004 and after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/1/2004 has been entered.

In the amendment filed 4/1/2004, several claims were amended (claims 1, 6-8, 13, 17-18, 21, 23, 25, 27). Claims 1-4, 6-11, 13-18, 21-23, 25 and 27 are pending and under consideration. Any rejection of record not addressed in this action is withdrawn. This action is not final.

New Claim Objections

Claim 1 is objected to because of the following informalities: the word "from" is misspelled as "Rom" in the next to last sentence of the claim. Appropriate correction is required.

Claim 4 is objected to because of the following informalities: the phrase "wherein each of the promoter sequences members comprises at least one" is grammatically incorrect. It would be remedial to simply delete the term "members" from the claim language. Appropriate correction is required.

Claim 17 is objected to because of the following informalities: the word "microorganism" is misspelled in line 3 of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-11, 13-15, 23, 25 & 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the office actions mailed 3/11/03 and 10/1/2003, and which are repeated below.**

The rejected claims are drawn to a set of promoters suitable for optimizing expression of a gene in a selected organism or group of organisms wherein the set of promoters comprise at least two consensus sequences where at least half of the consensus sequences are kept constant across the promoter set. The set of promoters must cover "a range of activities" of "a" gene in small steps, each step changing the promoter activity by 50-100%. For prokaryotic promoters, the conserved sequences can be selected from the group consisting of TATAAT, TTGACA and an activator binding sequence upstream of the TATAAT sequence. For eukaryotic organisms, the at least two consensus sequences being selected from the group consisting of a TATA-box and a UAS upstream of the TATA-box, and where the promoter set further has a randomized spacer sequence between the two consensus sequences or flanking at least one of the conserved sequences. Claims 18-20 are drawn towards methods of using subsets of promoter sequences obtained from the first set of promoter sequences to drive expression of a desired gene in

an organism or groups of organisms, or to control the flux of a metabolite in the desired organism or group of organisms.

The rejected claims thus comprise a set of promoters that can be derived from any source to drive expression of any gene in any organism (e.g. humans, archaebacteria, etc.) or any combination of organisms (e.g. meeting the claim's functional limitations in both humans and fish, or humans and S. aureus). The upstream activator sequences can be literally of any type. The set of promoters must drive expression of the operably linked gene to a particular range of any possible range of activities. Functionally, the set of promoters must cover the range of expression in steps of 50-100%. Thus, the rejected claims encompass an incredibly enormous genus of promoter sets that must meet very specific functional limitations (i.e. expression of a gene in a particular organism, or combination of organisms, in steps of 50-100% change in activity levels). For example, the limitation of covering the range of expression in steps of 50-100% greatly increases the description problems for the rejected claims. If one stipulates a single range of promoter activity for the claimed promoter set as from 1-100 units/hour, one can cover the range in steps of ~25 units/hour, ~10 units/hour, ~2 units/hour, etc. Thus, for every range of promoter activity, one can traverse the range in steps of 50-100% changes in activity in many different ways. Each of these different ways of traversing a given range of activity is likely to involve a series of different promoter constructs, each set possessing a different collection of promoters having different changes in the promoter sequence/structure. Given that the range of activities encompassed by the instant claims is any that is biologically possible, and that the claims encompass regulating the expression of literally any gene in any single organism, or combination of different

organisms, the genus of promoter sets encompassed by the rejected claims is so broad as to be incalculable.

The instant specification describes consensus promoter sequences observed in a few different prokaryotic or eukaryotic microorganisms (e.g. *L. lactis, E. coli, S. cerevisiae*) and describes experiments wherein a range of different promoter activities in different microorganisms is obtained. There is no description in the specification as originally filed of any promoter set that would meet the claim limitations in any particular multi-cellular organism (e.g. humans). While the range of activity obtained in some cases is impressive (e.g. Example1 and Figure 1), it is not clear from reading the examples and the legends to the figures that the promoter sets described necessarily meet the claim limitations (i.e. wherein half of at least two consensus sequences in at least two promoters in the library of promoters are conserved and wherein the at least two promoters only differ in activity by 50-100%). For example, the activities shown in Figures 1 & 3 are given on a logarithmic plot with no clear indicate that any two "adjacent" promoters necessarily meet the structural/functional limitations of the claim (e.g. on the logarithmic scale shown in these figures a difference in activity for "adjacent" promoters having 2-fold or 100% difference in activity cannot be clearly determined).

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of expression of a single gene in a single microorganism over, at best, a few possible ranges wherein the promoters within the set meet the functional limitations of the claims (e.g. a few possible subsets within the broader range of activities shown in Figure 1). The results described are not necessarily predictive of

promoter set structure for expression of different genes in the same organism (e.g. differences in transcription rates, transcript stability, etc.) or for the expression pattern of a given promoter set in a different organism. This is especially true for combinations of different organisms. For example, while certain promoter elements may be somewhat conserved across species lines (e.g. a TATA box), upstream activator binding sites of the invention would necessarily be expected to vary across species lines (e.g. human and shrimp), making it impossible for one to extrapolate from the few promoters described herein those promoter sets that would necessarily meet the functional/structural characteristics of the rejected claims. The prior art also does not appear to provide a reliable basis for one of skill in the art to envision promoter sets that will necessarily meet the structural/functional limitations of the rejected claims for a given gene in an organism or groups of organisms.

There remains no structural/functional basis for one of skill in the art to envision those promoter sets that 1) retain the conserved sequences and 2) satisfy the functional limitations of the claim with regard to step-wise increments in promoter activity amongst the members of the promoter set for the incredibly broad genus of such promoter sets encompassed by the rejected claims (i.e. literally any combination of activity range, gene and organism, or combination of organisms). Therefore, one of skill in the art would not have been able to envision a representative number of specific promoter sets to describe the broad genus of promoter sets encompassed by the rejected claims. One of skill in the art would thus have reasonably concluded applicants were not in possession of the claimed invention for claims 1-15, 18-21, 23, 25 and 27.

Response to Arguments/112 1st Written Description

Applicant's arguments filed in the response of 4/1/2004 have been fully considered but they are not persuasive. The response essentially argues: **1)** the instant specification provides examples of different promoter sets for different microorganisms including *L. lactis, S. cerevisiae, B. subtilis, Pseudomonas* and yeast (e.g. Examples 1 & 2, Example 7), **2)** claim 1 has been amended to recite a Markush group of different microorganisms, and **3)** the claims also recite specific conserved sequences, 4) the claims specifically recite structural characteristics (dsDNA sequences comprising conserved motifs) as well as functional characteristics (i.e. range of promoter activities in steps, each step changing the promoter activity by 50-100%, a set of selected sequences that optimize expression of a gene in a selected microorganism).

With regard to limiting the selected microorganisms encompassed by the claims to a Markush group of microorganisms (including lactic acid bacteria, *Bacillus, E. coli, Pseudomonas* and yeast), no such amendment has been entered. Thus, applicants are arguing a limitation that is not in the present claims. The claims still encompass an enormous genus of bacteria, fungi, thermophiles, protists, etc. While the examiner has in fact conceded that certain conserved promoter/enhancer sequences among a limited set of microorganisms has been described, there is no basis provided by the instant specification and prior art for one to be able to envision the particular alterations in a given promoter operatively linked to a given coding sequence for use in a given microorganism that will meet the functional limitations of the claims. Further, the claims are directed to undefined upstream activator-binding elements that have been modified to achieve the functional limitations of the claims. There is simply no basis for the skilled artisan to

envision what those upstream activator-binding elements will be for a given promoter/coding sequence/microorganism and the changes required to the promoter in those cased to meet the functional limitations of the claims with regard to promoter set activity. Further, applicants' arguments still have not addressed the issue of the many different expression ranges embraced by the claims for expression of a single gene in a single organism, or the issue of how different genes are expressed based upon other factors (e.g. differences in RNA structure, etc.). The specification has provided no guidance with regard to what the promoter sets would look like in any number of different microorganisms and still satisfy the functional limitations of the claims (e.g. in protozoa or in thermophyllic bacteria, etc.). It remains unclear that the few examples given in the specification actually meet the functional limitations of the claims for any given gene.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-4, 6-11, 13-18, 21, 23, 25 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections.**

Claims 1, 16 and 18 recite the limitation "at least two consensus sequences selected from the group consisting of" and then recite "**an** activator binding site upstream" or "**a** UAS upstream of" (examiner's emphasis added). It is unclear as the claims are written whether the recited Markush group includes embodiments where two

upstream sequences are the two members of the Markush group that selected since the claim language as written appears to embrace multiple upstream elements.

Claim 18 recites in the first line of part (i), "selecting from a set of promoter sequences" and then goes on at length to describe the characteristics of the set of promoter sequences from which a selection is made. It is unclear, however, as the claim is written what is actually selected in part (i) of the claim. It would be remedial to amend the claim to make clear what, if anything, is selected from the promoter set of part (i) of the claim.

Claim 3 is vague and indefinite in that the metes and bounds of the phrase "wherein each of the promoter sequences comprises a regulatory DNA sequence imparting a specific regulatory feature to each of the promoter sequences" are unclear. It is unclear what is intended by the term "specific regulatory feature" as it does not appear to be explicitly defined in the specification. Further, it is unclear how each regulatory feature is intended to be specific. For example, does the cited phrase mean that each promoter sequence in the promoter set has a unique feature, distinct from all other members of the set? Or does the set comprise a regulatory feature that is unique to the set of promoters as compared to other promoter sets?

Claim 14 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "the promoter sequence" in claim 1, upon which claim 14 is dependent.

Claim 21 is vague and indefinite in that the metes and bounds of the term "pathway" are unclear. The term is unclear in that it is undefined in the claim as to what kind of pathway is contemplated. Claim 21 is further vague and indefinite in that there is

no clear and antecedent basis for the term "the cellular metabolite". It would be remedial to amend the claim to clearly indicate that the at least one gene is a gene in a metabolic pathway and that it is the gene product whose expression level is changed. Finally, there is no clear and positive antecedent basis for the term "the clone" in part (iv) of the claim.

Conclusion

Claims 1-4, 6-11, 13-18, 21-23, 25 and 27 are pending. Claim 22 is allowed.

Claims 1-4, 6-11, 13-18, 21, 23, 25 and 27 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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